Publications

REiNS Publications

REiNS has published recommendations in three supplements in the journal *Neurology* and one in the journal *Clinical Trials*. Click these links to access the full supplements:

Supplement I (2013)

Supplement II (2016)

Supplement III (2021)

Supplement IV (2024)

Below is a list of the articles published in these supplements organized by topic. Click each topic to jump to the articles:

NF1—Neurofibromatosis type 1

NF2—*NF2*-related schwannomatosis (formerly called neurofibromatosis type 2)

SWN—*SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, schwannomatosis-NOS (not otherwise specified), or schwannomatosis-NEC (not elsewhere classified)

REiNS Publications Listed by Topic:

About REiNS

Achieving consensus for clinical trials: The REiNS International Collaboration

Plotkin SR, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, Widemann BC. Achieving consensus for clinical trials: the REiNS International Collaboration. *Neurology*. 2013;81(21 Suppl 1):S1-5; doi:10.1212/01.wnl.0000435743.49414.b6

> *Most early NF clinical trials used study designs similar to those used in cancer trials; however, because of differences in disease symptoms and tumor growth compared to solid cancers, there is a need for new designs that are better suited to NF. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 to reach agreement within the NF community about the design of future trials, with an emphasis on measures of response to treatment, also known as endpoints. This paper is an introduction to the first REiNS supplement published in 2013, which includes the first series of recommendations by the REiNS Collaboration.*

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Conclusions and future directions for the REiNS International Collaboration

Widemann BC, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, Plotkin SR. Conclusions and future directions for the REiNS International Collaboration. *Neurology*. 2013;81(21 Suppl 1):S41-4; doi:10.1212/01.wnl.0000435748.79908.c5

> *This paper is the conclusion to the first REiNS supplement published in 2013. It summarizes the first series of recommendations, addresses how they should be used in the context of NF clinical trials, and discusses future recommendations under development.*

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Consensus for NF clinical trials: Recommendations of the REiNS collaboration (Supplement II)

Widemann BC, Plotkin SR. Consensus for NF clinical trials: Recommendations of the REiNS collaboration (Supplement II). *Neurology*. 2016;87(7 Supplement 1):S1-S3; doi:10.1212/WNL.0000000000002930

> *This paper is an introduction to the second REiNS supplement published in 2016, which provides an update on clinical trials that have used the recommended measures from the first supplement. It also summarizes new recommendations for additional measures of response to treatment (endpoints) included in the rest of the supplement.*

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Neurofibromatosis Clinical Trials, REiNS Collaboration 2020 Recommendations: Looking Back and Moving Ahead

Gross AM, Plotkin SR, Widemann BC, on behalf of the REiNS International Collaboration. Neurofibromatosis Clinical Trials, REiNS Collaboration 2020 Recommendations: Looking Back and Moving Ahead. *Neurology.* 2021;97(7 Supplement 1):S1-S3; doi:10.1212/WNL.0000000000012429

> *This introduction to the third REiNS supplement published in 2021 provides a table of past REiNS recommendations and introduces the topics covered within the rest of the supplement. It also includes reflections on the use of REiNS Criteria in the FDA approval of the first medication for NF1 (Selumetinib) and what we have learned from that experience.*

Full Text (Web) **Full Text (PDF)** **NF1 NF2 SWN**

Biomarkers

Current status and recommendations for biomarkers and biobanking in neurofibromatosis

Hanemann CO, Blakeley JO, Nunes FP, Robertson K, Stemmer-Rachamimov A, Mautner V, Kurtz A, Ferguson M, Widemann BC, Evans DG, Ferner R, Carroll SL, Korf B, Wolkenstein P, Knight P, Plotkin SR, on behalf of the REiNS International Collaboration. Current status and recommendations for biomarkers and biobanking in neurofibromatosis. *Neurology*. 2016;87(7 Suppl 1):S40-8; doi:10.1212/WNL.0000000000002932

> *This paper describes the existing biomarkers in NF, recommends standard operating procedures (SOPs) for the collection of biological samples in NF, and recommends the clinical information that should accompany all samples.*

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical Use

Bettegowda C, Upadhayaya M, Evans DG, Kim A, Mathios D, Hanemann CO, on behalf of the REiNS International Collaboration. Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical Use. *Neurology*. 2021;97(7 Suppl 1):S91-S98; doi:10.1212/WNL.0000000000012436

> *The goal of this paper was to determine how genotype-phenotype correlations (the relationship between a person's genetic mutation and symptoms) can be used in clinical trials and clinical consultations for NF1 and NF2. For NF1, more information is needed to determine how this should impact clinical care and clinical trials. For NF2, REINS recommends grouping patients by genetic severity score for clinical trials.*

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2**

Cutaneous Neurofibromas

Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials

Cannon A, Pichard DC, Wolters PL, Adsit S, Erickson G, Lessing AJ, Li P, Narmore W, Röhl C, Rosser T, Widemann BC, Blakeley JO, Plotkin SR, on behalf of the REiNS International Collaboration. Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S15-S24; doi:10.1212/WNL.0000000000012425

This paper presents a survey exploring the experiences of NF1 adults with cutaneous neurofibromas, taking into account their location, size, color, pain, and itchiness. The survey also asked patients' opinions about treatment options, what would be considered a successful treatment, and what side effects would be acceptable.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1

Maguiness S, Berman Y, Rubin N, Dodds M, Plotkin SR, Wong C, Moertel C, on behalf of the REiNS International Collaboration. Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1. *Neurology*. 2021;97(7 Suppl 1):S25-S31; doi:10.1212/WNL.0000000000012427

This paper explores the use of the Skindex, a general dermatology questionnaire, to assess the effects of skin conditions on people with NF1 in the US and Australia. The study showed that NF1-related skin issues may negatively impact physical, emotional, and functional aspects of quality of life (QOL), with features such as the number of cutaneous neurofibromas (cNFs), female sex, and the presence of facial cNFs being most associated with lower scores. It also highlighted the need to design more specific NF1 skin-related QOL measures.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Validating Techniques for Measurement of Cutaneous Neurofibromas: Recommendations for Clinical Trials

Thalheimer RD, Merker VL, Ly KI, Champlain A, Sawaya J, Askenazi NL, Herr HP, Da JLW, Jordan JT, Muzikansky A, Pearce EM, Sakamoto FH, Blakeley JO, Anderson RR, Plotkin SR, on behalf of the REiNS International Collaboration. Validating Techniques for Measurement of Cutaneous Neurofibromas: Recommendations for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S32-S41; doi:10.1212/WNL.0000000000012428

Researchers evaluated three techniques to measure cutaneous neurofibromas (cNFs): high-frequency ultrasound, 3D photography, and digital calipers. Within each technique, the measurements were consistent with repeated testing. Considerations for choosing which method to use for clinical trials include: cNF size, cNF type, cost, and time to perform measurements.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Status and Recommendations for Incorporating Biomarkers for Cutaneous Neurofibromas Into Clinical Research

Wallis D, Stemmer-Rachamimov A, Adsit S, Korf B, Pichard D, Blakeley J, Sarin KY, on behalf of the REiNS International Collaboration. Status and Recommendations for Incorporating Biomarkers for Cutaneous Neurofibromas Into Clinical Research. *Neurology*. 2021;97(7 Suppl 1):S42-S49; doi:10.1212/WNL.0000000000012426

REiNS reviewed existing data on cutaneous neurofibroma (cNF) biomarkers to assess their usefulness in clinical trials. Their investigation concluded that there is a lack of validated cNF biomarkers and made recommendations for future research.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Functional Outcomes

Functional outcome measures for NF1-associated optic pathway glioma clinical trials

Fisher MJ, Avery RA, Allen JC, Ardern-Holmes SL, Bilaniuk LT, Ferner RE, Gutmann DH, Listernick R, Martin S, Ullrich NJ, Liu GT, for the REiNS International Collaboration. Functional outcome measures for NF1-associated optic pathway glioma clinical trials. *Neurology*. 2013;81(21 Suppl 1):S15-24; doi: 10.1212/01.wnl.0000435745.95155.b8

For patients with NF1-associated optic pathway gliomas (OPG), the main goal of treatment is maintaining or improving vision. Therefore, the success of a treatment for OPG should be primarily based on measures of vision rather than changes in tumor size. REiNS recommends visual acuity, which is how well someone can see, as the best measure (or primary endpoint) for use in clinical trials in children with OPG. This paper also recommends the best methods for measuring visual acuity in children and reviews the suitability of other measures of vision as secondary endpoints for clinical trials.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Hearing and facial function outcomes for neurofibromatosis 2 clinical trials

Plotkin SR, Ardern-Holmes SL, Barker FG, Blakeley JO, Evans DG, Ferner RE, Hadlock TA, Halpin C, for the REiNS International Collaboration. Hearing and facial function outcomes for neurofibromatosis 2 clinical trials. *Neurology*. 2013;81(21 Suppl 1):S25-32; doi: 10.1212/01.wnl.0000435746.02780.f6

Hearing loss and facial weakness are important functional outcomes for NF2 clinical trials; however, there was a lack of agreement concerning how to measure responses to treatment. REiNS recommends the use of maximum word recognition score as a primary hearing outcome measure. The group also recommends the scaled measurement of improvement in lip excursion (SMILE) system as a primary outcome measure for studies of facial function.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF2**

Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1

Plotkin SR, Davis SD, Robertson KA, Akshintala S, Allen J, Fisher MJ, Blakeley JO, Widemann BC, Ferner RE, Marcus CL, for the REiNS International Collaboration. Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1. *Neurology*. 2016;87(7 Suppl 1):S13-20; doi: 10.1212/WNL.0000000000002933

Airway function and sleep are important functional outcome measures for people with NF1-related airway plexiform neurofibromas. REiNS recommends using the Apnea Hypopnea Index (AHI) for measuring sleep quality and using either airway resistance calculations or forced expiratory volume for measuring airway function in NF1 clinical trials.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Reliability of Handheld Dynamometry to Measure Focal Muscle Weakness in Neurofibromatosis Types 1 and 2

Akshintala S, Khalil N, Yohay K, Muzikansky A, Allen J, Yaffe A, Gross AM, Fisher MJ, Blakeley JO, Oberlander B, Pudel M, Engelson C, Obletz J, Mitchell C, Widemann BC, Stevenson DA, Plotkin SR, on behalf of the REiNS International Collaboration. Reliability of Handheld Dynamometry to Measure Focal Muscle Weakness in Neurofibromatosis Types 1 and 2. *Neurology*. 2021;97(7 Suppl 1):S99-S110; doi:10.1212/WNL.0000000000012439

Muscle weakness may be seen in many patients with NF1 and NF2, either due to nerve sheath tumors or other reasons. A handheld dynamometer (HHD) is a device that allows for the objective measurement of muscle strength. The study found that when used by a trained examiner following a standard protocol, HHD is a reliable device that can be used in future clinical trials for patients with NF1 and NF2.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2**

Imaging

Recommendations for imaging tumor response in neurofibromatosis clinical trials

Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, Barker FG, Connor S, Evans DG, Fisher MJ, Goutagny S, Harris GJ, Jaramillo D, Karajannis MA, Korf BR, Mautner V, Plotkin SR, Poussaint TY, Robertson K, Shih CS, Widemann BC, for the REiNS International Collaboration. Recommendations for imaging tumor response in neurofibromatosis clinical trials. *Neurology*. 2013;81(21 Suppl 1):S33-40; doi:10.1212/01.wnl.0000435744.57038.af

Standardized criteria commonly used in clinical trials for cancers are not practical to assess benign NF-related tumors, such as plexiform neurofibromas or vestibular schwannomas. These tumors can have complex shapes and grow relatively slowly, therefore more sensitive methods are needed to detect change. REiNS recommends using 3D volume measurements from MRI to define response in clinical trials. This paper also specifies how these MRIs should be obtained and proposes criteria for assessing tumor growth or shrinkage over time.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Current whole-body MRI applications in the neurofibromatosis: NF1, NF2, and schwannomatosis

Ahlawat S, Fayad LM, Khan MS, Bredella MA, Harris GJ, Evans DG, Farschtschi S, Jacobs MA, Chhabra A, Salamon JM, Wenzel R, Mautner VF, Dombi E, Cai W, Plotkin SR, Blakeley JO. Current whole-body MRI applications in the neurofibromatoses: NF1, NF2, and schwannomatosis. *Neurology*. 2016;87(7 Suppl 1):S31-9; doi:10.1212/WNL.0000000000002929

Whole-body MRI (WB-MRI) can identify and measure internal tumors in people with neurofibromatosis and schwannomatosis (NF/SWN). REiNS reviewed the literature to assess the best method of performing and interpreting WB-MRI so it can be used as a tool in NF/SWN clinical trials. Although there are many ways of performing WB-MRI, the REiNS group agreed that a specific technique called STIR should be included as a core sequence to allow for consistent tumor measurement.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment

Ahlawat S, Ly KI, Fayad LM, Fisher MJ, Lessing AJ, Berg DJ, Salamon JM, Mautner VF, Babovic-Vuksanovic D, Dombi E, Harris G, Plotkin SR, Blakeley J, on behalf of the REiNS International Collaboration. Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment. *Neurology*. 2021;97(7 Suppl 1):S111-S119; doi:10.1212/WNL.0000000000012437

REiNS surveyed NF1 clinicians about their use of imaging to identify and monitor plexiform neurofibromas (PNs) in patients with NF1. Regional (localized) MRI was consistently used for patients with known PN or symptoms of a PN. However, there was a wide variety of approaches to screening asymptomatic patients with no known PN. This supports the need to establish guidelines on when and how to image NF1 patients to diagnose and monitor PNs.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Neurocognitive Outcomes

Neurocognitive outcomes in neurofibromatosis clinical trials: Recommendations for the domain of attention

Walsh KS, Janusz J, Wolters PL, Martin S, Klein-Tasman BP, Toledo-Tamula MA, Thompson HL, Payne JM, Hardy KK, de Blank P, Semerjian C, Gray LS, Solomon SE, Ullrich N, for the REiNS International Collaboration. Neurocognitive outcomes in neurofibromatosis clinical trials: Recommendations for the domain of attention. *Neurology*. 2016;87(7 Suppl 1):S21-30; doi:10.1212/WNL.0000000000002928

The goal of this paper is to identify standardized and specific cognitive assessment tools for use in measuring attention in school-aged children with NF1. The Digit Span subtest from the Wechsler scales was the recommended performance measure of attention. The Conners scales were the recommended measure of behavioral problems associated with attention.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Recommendations for Social Skills End Points for Clinical Trials in Neurofibromatosis Type 1

Janusz JA, Klein-Tasman BP, Payne JM, Wolters PL, Thompson HL, Martin S, de Blank P, Ullrich N, Del Castillo A, Hussey M, Hardy KK, Haebich K, Rosser T, Toledo-Tamula MA, Walsh KS, on behalf of the REiNS International Collaboration. Recommendations for Social Skills End Points for Clinical Trials in Neurofibromatosis Type 1. *Neurology*. 2021;97(7 Suppl 1):S73-S80; doi:10.1212/WNL.0000000000012422

Many children and adolescents with NF1 have difficulty with various aspects of social functioning. REiNS reviewed and evaluated current literature for outcome measures of social skills in people ages 6-18. The Social Skills Improvement System-Rating Scales (SSIS-RS) was recommended for clinical trials focusing on broad social functioning, while the Social Responsiveness Scale, Second Edition (SRS-2), was recommended for studies on problematic social behaviors associated with autism spectrum disorder.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis

Klein-Tasman BP, Lee K, Thompson HL, Janusz J, Payne JM, Pardej S, de Blank P, Kennedy T, Janke KM, Castillo AD, Walsh KS, on behalf of the REiNS International Collaboration. Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis. *Neurology*. 2021;97(7 Suppl 1):S81-S90; doi:10.1212/WNL.0000000000012423

This paper is a review of current performance-based and observer-rated measures of attention in preschool-aged children with NF1. In contrast to the recommendations for school-aged children, the Attention Deficit Hyperactivity Disorder Rating Scale was recommended for preschoolers; additional measures were recommended as secondary outcomes. It also provides practical guidelines for clinical trials targeting this age group.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1**

Patient Engagement

Enhancing Neurofibromatosis Clinical Trial Outcome Measures Through Patient Engagement: Lessons From REiNS

Merker VL, Lessing AJ, Moss I, Hussey M, Oberlander B, Rose T, Thalheimer R, Wirtanen T, Wolters PL, Gross AM, Plotkin SR, on behalf of the REiNS Int ernational Collaboration. Enhancing Neurofibromatosis Clinical Trial Outcome Measures Through Patient Engagement: Lessons From REiNS. *Neurology*. 2021;97(7 Suppl 1):S4-S14; doi:10.1212/WNL.0000000000012430

The REINS patient representative program began in fall 2017 to include patients with NF1, NF2, and schwannomatosis and their family members in clinical trial design. This paper shows the positive impact patient representatives had on REiNS, including how they worked with researchers to develop better clinical trial outcome measures. It also discusses what made it easier or harder for patient representatives to participate in REiNS.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Patient-Reported Outcomes

Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials

Wolters PL, Martin S, Merker VL, Gardner KL, Hingtgen CM, Tonsgard JH, Schorry EK, Baldwin A, for the REiNS International Collaboration. Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials. *Neurology*. 2013;81(21 Suppl 1):S6-14; doi:10.1212/01.wnl.0000435747.02780.bf

REiNS developed a systematic process to rate existing patient-reported outcomes for use in NF clinical trials. Using this process, they reviewed measures of pain intensity and recommended using the Numerical Rating Scale (NRS-11), a 0-10 pain scale.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Patient-reported outcomes of pain and physical functioning in neurofibromatosis clinical trials

Wolters PL, Martin S, Merker VL, Tonsgard JH, Solomon SE, Baldwin A, Bergner AL, Walsh K, Thompson HL, Gardner KL, Hingtgen CM, Schorry E, Dudley WN, Franklin B, for the REiNS International Collaboration. Patient-reported outcomes of pain and physical functioning in neurofibromatosis clinical trials. *Neurology*. 2016;87(7 Suppl 1):S4-S12; doi:10.1212/WNL.0000000000002927

Measuring whether new treatments impact how people feel and function is important for regulatory approval. REiNS reviewed existing measures of pain interference to determine which ones were best suited for NF clinical trials. The group recommended the Pain Interference Index for children /adolescents and the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale for adults. The group also reviewed measures of physical functioning and recommended the PROMIS Physical Functioning Scale for all ages.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**

Patient Report of Hearing in Neurofibromatosis Type 2: Recommendations for Clinical Trials

Thompson HL, Blanton A, Franklin B, Merker VL, Franck KH, Welling DB, on behalf of the REiNS International Collaboration. Patient Report of Hearing in Neurofibromatosis Type 2: Recommendations for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S64-S72; doi:10.1212/WNL.0000000000012424

Changes in hearing are typically measured with audiology testing in NF2 clinical trials, but there is also a need to understand if people with NF2 personally feel their hearing and quality of life (QOL) has improved due to experimental treatments. REiNS reviewed existing patient-reported measures of hearing function and hearing-related QOL, and recommended the Self-Assessment of Communication (SAC) for use in future NF2 clinical trials.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF2**

Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials

Wolters PL, Vranceanu AM, Thompson HL, Martin S, Merker VL, Baldwin A, Barnett C, Koetsier KS, Hingtgen CM, Funes CJ, Tonsgard JH, Schorry EK, Allen T, Smith T, Franklin B, Reeve S, on behalf of the REiNS International Collaboration. Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S50-S63; doi:10.1212/WNL.0000000000012421

This paper reviews existing patient-reported measures of quality of life for use in NF clinical trials. The group recommended several generic measures of quality of life (QOL) depending on the ages of the patients and purpose of the trial. For disease-specific measures of quality of life, the group recommended the Pediatric Quality of Life Inventory (PedsQL) NF1 module for NF1 trials and the NF2 Impact on Quality of Life (NFTI-QOL) for NF2 trials.

Abstract **Full Text (Web)** **Full Text (PDF)** **NF1 NF2 SWN**